

Top Ten Tips Palliative Care Clinicians Should Know About Medical Cannabis

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Abstract

The use of medical cannabis is increasing significantly throughout the United States in spite of limited and sometimes contradictory data about its effectiveness. Palliative care providers are being asked to consider cannabis as part of symptom-directed treatment regimens although many providers have limited experience recommending medical cannabis and were trained before it was commercially available. This article seeks to dispel myths about medical cannabis and provides a balanced view of the benefits and burdens of this therapeutic option, providing evidence where it exists and offering practicing clinicians guidance on conditions in which medical cannabis is likely to be helpful or burdensome.

Keywords: cannabinoids; medical cannabis; medical marijuana; palliative care; route of administration; symptom control

Introduction

HIGH-QUALITY PALLIATIVE CARE (PC) practice requires incorporating novel and evolving supportive care treatments into the routine care of patients with serious illness. A growing conversation in the profession centers around the potential role of medical cannabis, paralleling several efforts across the country to approve and legalize medical cannabis use.¹ At the federal level, cannabis remains illegal, including continued designation by the Food and Drug Administration (FDA) as a Schedule I drug. In contrast, many states are moving away from decriminalization to actively promoting various amounts and formulations of cannabis for medical and/or recreational purposes.² Coupled with an evolving evidence base, clinicians face challenges to stay current with changes in regulatory approvals and clinical best practices. Further complicating PC practice is the relative scarcity of evidence, guidance, and best practices to guide clinicians in prescribing and managing these medications (e.g., dose, route of administration, timing of administration, and interactions).

Any discussion of cannabis must start with clarifying nomenclature. Depending upon settings, products are referred to by various names, including “medical marijuana,” “medical cannabis,” “cannabis,” “marijuana,” “cannabinoids,” and the individual chemical components of cannabis such as tetrahydrocannabinol (THC) and cannabidiol (CBD). Adding to

this confusion are the many routes of administration, the criminalized and stigmatized history of marijuana use, and clinicians’ greater familiarity with cannabis as a substance of abuse (marked by the diagnosis of “cannabis use disorder” in the fifth edition of the *Diagnostic and Statistical Manual*). This may lead clinicians to avoid discussing cannabis use with their patients, remain biased against medical cannabis where evidence for its use exists, or, under the sway of public opinion, prematurely adopt cannabis as a treatment even where evidence is lacking.

For the purposes of this review, we will refer to “medical cannabis” as those products that contain cannabinoids and are used for medical indications. There are three medications that are themselves cannabinoids: dronabinol (synthetic THC), nabilone (a synthetic cannabinoid similar to THC), and nabiximols (a combination of CBD and THC not available in the United States). CBD was also recently approved by the FDA in the United States under the brand name Epidiolex for the management of refractory pediatric epilepsy, although off-label use has been described in chemotherapy-induced neuropathy, social phobia, and psychosis.^{3–5} Other synthetic cannabinoids exist that are substances of abuse and are not the focus of this review (e.g., “K2” and “spice”). These differentiations are nevertheless important to make so clinicians have a clearer understanding of the landscape of cannabinoid use and misuse. Herein we present our thoughts

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on the top 10 tips to familiarize PC clinicians with this rapidly evolving space.

Tip 1: Local Laws and Regulations Vary Regarding Medical Cannabis

It remains a federal crime to sell or transport cannabis because it is a Schedule I substance. Nevertheless, 33 states, in addition to the District of Columbia, Guam, and Puerto Rico, have legalized medical cannabis and 10 of those have legalized recreational cannabis as well.^{2,6} The National Conference of State Legislatures regularly updates a map delineating medical cannabis laws.² Notably, clinicians and pharmacies within the Veterans Affairs health system cannot recommend or dispense medical cannabis since federal law overrides any state regulation. However, veterans will not lose Veterans Administration (VA) access or benefits because they participate in a state-level medical cannabis program.⁷ Regulation varies from state to state as to how much medical cannabis patients may possess and how it can be obtained (e.g., personally grown vs. obtained from a dispensary). Patients should exercise caution when purchasing cannabis online as there may be less oversight resulting in potentially diminished purity.⁸

Regulations also vary regarding clinicians' involvement in how patients obtain medical cannabis. Unlike other substances obtained with a clinician's approval, medical cannabis is usually not prescribed. Rather, an appropriate clinician must certify that a patient has a *qualifying condition* before the patient can obtain medical cannabis from a dispensary. Qualifying conditions vary by state and range from pain to nausea to cancer. Unfortunately, patients are sometimes left to experiment with dose and route of administration, relying on recommendations from friends, media, the dispensary, and sometimes the clinician who certified their qualifying condition.

Tip 2: A Comprehensive Pain Assessment Includes Asking About Cannabis Use

One of the indications for medical cannabis with the most evidence is controlling pain.^{6,9} At least part of the impetus for the scientific study of cannabis has been the use of illicit cannabis to improve pain, which for the majority of users is effective.¹⁰ Cannabinoid receptors are present in afferent nerves that respond to painful stimuli and are also found in parts of the brain associated with analgesia (e.g., periaqueductal gray, raphe nuclei, and central-medial thalamic nuclei), suggesting a possible therapeutic role in pain management, both synergistically with the opioid system and independent of it.^{11,12}

Patients may have experiences using variable amounts and routes of administration of cannabis in an attempt to treat their own pain. They may also have had particular adverse effects to the recreational use of cannabis (e.g., paranoia, dry mouth, and sedation) that may inform plans regarding the use of medical cannabis. Clinicians who practice in states where medical cannabis is legal should be particularly attuned to this as nonmedical use of cannabis increases when medical cannabis is legalized.¹³ Because pain in PC settings is often managed with opioids, a comprehensive pain assessment must include investigation of nonmedical and medical uses of cannabis as well as other substances. Cannabis has neuro-

psychiatric side effects; therefore, screening for psychological conditions such as depression, anxiety, and a history of psychosis is also indicated. Studies have not supported the use of cannabis in treating depression and, furthermore, use of cannabis in the context of cannabis use disorder (vs. medical cannabis use, about which we have less evidence) is associated with other psychiatric conditions such as depression.^{9,14} Therefore, cannabis use should be investigated before the prescription of opioids or certifying of a qualifying condition for medical cannabis.

Medical cannabis use (or illicit cannabis use for self-treatment purposes) presents a challenge for concomitant opioid prescribing. When clinicians discover, either through history or drug testing, that a patient is using cannabis, they should explore the reasons for use and probe for use of other illicit substances. True to the "gateway drug" paradigm, illicit cannabis use is associated with illicit use of other substances, which may cause more serious adverse interactions with opioids.¹⁵ Such illicit use may also place opioids in the hands of those individuals who can divert them (or associate with those likely to steal and divert them) and cause patient and societal harm. Physiologically, although concomitant use of medical cannabis use has been associated with a synergistic effect on analgesia without altering opioid levels, such evidence must be applied with caution as the psychoactive effects, particularly sedation, may also be synergistic.¹⁶ Therefore, a urine drug screen that is unexpectedly positive for THC should prompt a conversation by clinicians about these concerns.

Tip 3: Medical Cannabis May Be Useful for the Treatment of Neuropathic Pain

Current evidence suggests that cannabis can provide modest relief of pain resulting from various etiologies in broad populations of patients.^{6,9,12} Most notably, among the various types and etiologies of pain, evidence is growing that medical cannabis is particularly effective in the management of various types of neuropathic pain (e.g., diabetic, traumatic, HIV, and chemotherapy).^{17–21} There is also evidence that synthetic cannabinoids, such as dronabinol 2.5–10 mg or nabilone 1–4 mg daily, can treat neuropathic pain.²² Evidence also supports the use of medical cannabis in relieving cancer-related pain, although the quantity of studies is smaller when compared with those focused on neuropathic pain.²³

The majority of these studies used inhaled cannabis at various doses and frequencies, and the ratio of THC to CBD in any given preparation may vary as well. This limits generalizability and confounds the anticipatory guidance clinicians may give their patients as there is no "standard" dose, route of administration, or formulation of medical cannabis for these applications. Finally, the results of these clinical studies cannot be extrapolated to patients who use illicitly procured cannabis for the purposes of pain management.

Tip 4: Medical Cannabis Can Be Used to Treat Chemotherapy-Induced Nausea and Vomiting

Chemotherapy-induced nausea and vomiting (CINV) used to be a disabling, sometimes treatment-limiting, side effect that has since been relieved significantly by the use of modern antiemetic regimens. Nevertheless, medications such as ondansetron, aprepitant, and others have their own side effects.

Anecdotal reports in managing refractory CINV with cannabis have provided some impetus for more thorough investigation.

Cannabinoids, including the prescribed agents dronabinol and nabilone, have been used for many years and are effective in treating CINV.^{9,24} The type of chemotherapy used may impact the antiemetic effectiveness of cannabinoids, as demonstrated by their positive effect on CINV from high-dose methotrexate, but not doxorubicin or cyclophosphamide.^{25,26} The emetogenicity of the regimen should be considered, as oral cannabinoids are effective but likely only as adjunctive agents in the setting of highly emetogenic chemotherapy.^{6,27} There is a dearth of high-quality evidence supporting the use of cannabinoids through other routes of administration for CINV. It also remains unclear what the appropriate ratio of THC to CBD might be in managing CINV, and if CBD alone can provide antiemetic effects. At best, then, cannabinoids are likely to provide adjunctive support to other agents in a patient's antiemetic regimen. Importantly, overuse of cannabis can result in cannabinoid hyperemesis syndrome (described as follows), but this has not been described with mild to moderate use in the medical setting.

Tip 5: Differences in Bioavailability Among Routes of Administration for Medical Cannabis Have Been Inadequately Studied for Medical Uses

Medical cannabis can be administered through smoking, vaporization ("vaping"), eating, tinctures, and salves. Each route of administration impacts the onset of action as well as the intensity and duration of effects. Smoking and vaporizing have similarly rapid onsets of action, reach peak blood levels within 30 minutes and then drop within 1 to 3.5 hours.⁶ Enteral administration of medical cannabis, in contrast, will result in a slower onset of action and a prolonged duration of effect. Notably, cannabinoids undergo first pass metabolism and their bioavailability is reduced when eaten. The first pass effect does not appear to apply to buccal administration in the form of sprays or lozenges. A patient's comorbidities may thus influence the preferred route of administration (e.g., preexisting lung disease may prefer edible route vs. smoking). Patients may also have preferred routes of administration they have discovered through experimentation.

Cannabinoids can interact with other medications, both pharmacokinetically and with synergistic side effects. For example, CBD increases levels of clobazam and clobazam-associated side effects in pediatric patients with epilepsy.²⁸ Because it is extensively protein-bound, THC (and other cannabinoids) may displace other medications and increase their effect. CBD is metabolized by CYP2C9, CYP2C19, and CYP3A4, and may be impacted by concomitant use of inducers and inhibitors of these enzymes.²⁹ Studies are limited, but at least one trial demonstrated that cannabinoids (specifically CBD) can be used without diminishing the efficacy of paclitaxel; this cannot be generalized to other chemotherapy or immunotherapy.³

Although these and other routes of administration are for recreational use of cannabis, they have not been individually or comparatively studied in medical applications.³⁰ Therefore, medical comorbidities may influence the effects of medical cannabis in unexpected ways and clinicians should

be vigilant for increased side effects or diminished effectiveness as a result. It is important to explore whether patients have had experience using cannabis through a particular route of administration, why they chose that route, and if another route is more appropriate. There may be other unique outcomes patients have experienced or else they should be advised may occur. For example, vaporizing cannabis oil may result in a higher dose of cannabinoids and subsequent adverse effects such as psychosis.

Tip 6: The Evidence for the Use of Cannabis in Psychiatric Illness Is Limited and Varied

Although some patients may claim that the use of cannabis helps their sleep, anxiety, or mood, an assessment of their psychiatric and substance use history may actually bear out that cannabis is *contributing to* rather than helping the problem. Therefore, differentiating substance-induced and independent psychiatric disorders is critical. Psychiatric illnesses are heterogeneous, and evidence in favor of one condition or symptom cannot be extrapolated to another condition or symptom. Furthermore, patients with psychiatric illness are themselves diverse, and often have histories complicated by substance abuse, childhood trauma, homelessness, and medical illness. Due to this variation, it can be difficult to design robust studies with results that are generalizable. Furthermore, the route of administration may impact efficacy. For instance, a short-acting effect from inhaled medical cannabis may differ in the management of a sleep disorder when compared with the longer-acting effect from eaten medical cannabis. Nevertheless, preclinical studies are promising.^{31,32}

Trials are underway examining the impact of medical cannabis in managing different aspects of post-traumatic stress disorder, as there is some evidence to suggest that cannabinoids may be helpful in decreasing the severity of nightmares.³² Although no trials exist that directly examine the use of medical cannabis in treating depression, some trials that used cannabinoids as an intervention for other problems (e.g., multiple sclerosis and chronic pain) measured depression as a secondary outcome and failed to demonstrate improvement in that domain.^{9,33,34} Medical cannabis is not beneficial in the management of dementia.^{6,35} One systematic review identified one trial that supported the use of CBD in reducing anxiety associated with public speaking.⁹ With the current evidence, we cannot recommend cannabinoids for pharmacologic management of psychiatric illness. Some patients may nevertheless claim benefit, in which case clinicians should document their use, frequency, amount, and monitor for side effects and medication interactions (e.g., increased somnolence with benzodiazepines or opioids).

Tip 7: Although Useful for the Treatment of Anorexia Associated with AIDS, There Is Little Evidence for the Use of Medical Cannabis in Cancer-Associated Cachexia and Anorexia

Some patients report that recreational use of cannabis improves their appetite, which provides an impetus for investigating whether medical cannabis can impact anorexia and weight loss. Dronabinol, a synthetic THC compound, is FDA approved for the treatment of HIV/AIDS-associated

anorexia and cachexia. Inhaled cannabis has also been shown to be effective in weight gain in HIV/AIDS.⁶

These improvements in anorexia and weight loss in HIV/AIDS have led researchers to investigate whether similar benefits can be seen in other conditions such as cancer. Unfortunately, evidence has revealed that medical cannabis is not effective for the treatment of cancer-associated anorexia and cachexia.^{6,36} This may be due to the pathophysiology of the anorexia itself, with the high metabolic rate of the cancer contributing at least in part to the overall weight loss of those patients. Furthermore, depending on the route of administration, medical cannabis may have side effects that further impair a patient's willingness to eat and enjoyment of eating (e.g., dry mouth). Given this evidence, we cannot recommend cannabinoids for the improvement of cancer-associated cachexia and anorexia.

Tip 8: Smoking Medical Cannabis Is Not Associated with Lung Cancer or Chronic Lung Disease, But Does Cause Side Effects

Since both tobacco and cannabis can both be smoked, there was initially concern that cannabis, when smoked, could also be associated with lung cancer and chronic lung disease. There are substantial differences in use between the two substances. For example, tobacco cigarettes are usually smoked in much greater quantity than cannabis cigarettes. Perhaps for this reason, there is no convincing evidence that the use of medical cannabis is linked with lung, head and neck, or esophageal cancers.^{6,37,38} There is, however, a link between chronic and frequent use of cannabis and the development of testicular cancer, particularly nonseminomas.³⁹ Although there is no convincing evidence that cannabis use leads to chronic obstructive pulmonary disease, there is a link between smoking cannabis and cough and bronchitis, which may be related to the irritating smoke itself rather than any active ingredient.⁴⁰ These effects make smoking a less appealing route of administration for those with chronic lung disease.

The most common adverse effects from medical cannabis, as opposed to recreational cannabis, include dizziness, dry mouth, nausea, euphoria, confusion, somnolence, and hallucinations.^{9,35} Those with preexisting cardiovascular disease may be at increased risk of myocardial infarction from medical cannabis use, which is important to consider when treating older adults.^{41,42} Most impressively, nausea, vomiting, and abdominal pain, a triad called “cannabinoid hyperemesis syndrome,” can result from chronic and frequent use of cannabis. This syndrome may be less of a risk when cannabis is used in an appropriate medical context.⁴³

Cannabis is abused for its neuropsychiatric effects, and these may be prominent with medical use as well. Diagnosing primary psychiatric disorders can be challenging when patients are using cannabis (either for recreational or medical use). Cannabis has been associated with depression and anxiety, although the evidence has not yet established a directional link: Are depressed or anxious patients more likely to use cannabis, or are those people who use cannabis more likely to become anxious or depressed?^{6,44} Cannabis's link with suicide is similarly unclear.⁴⁵ Medical cannabis can impair memory and attention as well as cause confusion and somnolence.⁴⁶ Psychosis is a well-known risk of recreational

use of cannabis and synthetic cannabinoids (including dronabinol) and may occur with other forms of medical cannabis as well.^{6,47,48} This reinforces the need for good clinical practice in monitoring for adverse effects of those substances a patient is ingesting.

Tip 9: Pediatric Epilepsy Is a New and Growing Indication for Medical Cannabis

As cannabinoids are effective in preventing seizures in animal models, there is hope they may have clinical applications for humans in epilepsy.⁴⁹ Furthermore, some people who use cannabis illicitly find that it helps their seizures, although there are cases of its effectiveness even with non-therapeutically low doses, suggesting that some data may be contaminated with nonepileptic seizures.⁵⁰ The two systematic reviews to date have not supported the use of medical cannabis for the treatment of seizures.⁵¹ Evidence is growing for the use of medical cannabis in treating seizures, particularly in children, and sometimes in refractory cases. CBD specifically may be useful in the management of seizures in those children with Dravet syndrome or Lennox–Gastaut syndrome at doses as high as 25–50 mg/kg per day.^{52,53} Given this evidence in both these syndromes, the FDA recently approved Epidiolex oral solution in these clinical situations.⁵⁴ The initial dose is 2.5 mg/kg twice daily by mouth and increased to a maintenance dose of 10 mg/kg twice daily.

As CBD inhibits CYP3A and CYP2C, which are responsible for the metabolism of several antiepileptic drugs, clinicians should monitor for toxicity of other drugs if a child is concomitantly taking CBD.⁵⁵ The long-term effects of medical cannabis on brain development in children have not been established. As is the consistent theme across trials examining the therapeutic applications of medical cannabis, the ratio of THC to CBD and other cannabinoids that provides the most therapeutic benefit in epilepsy has yet to be discerned.

Tip 10: Cannabis Use Is Associated with an Increased Risk of Motor Vehicle Collision, and This Link Can Likely Be Extrapolated to Medical Cannabis

Although there is no evidence to support that cannabis can be lethal in overdose, driving while under the influence of cannabis is associated with a 20%–30% higher odds of a motor vehicle collision (MVC).⁵⁶ Some studies that have investigated this relationship identified those people who were reportedly driving under the intoxication of cannabis as actually driving with a recent or prior history of using cannabis but without acute intoxication. No studies have investigated the relationship between medical cannabis use specifically and MVC. However, medical cannabis does have neuropsychiatric side effects that could impair driving, including impaired attention, dizziness, confusion, and somnolence.^{9,46,57} Given that time to peak effect can vary depending on the route of administration and the particular composition of cannabinoids, it is difficult to make a general recommendation as to how long after taking medical cannabis patients should avoid using heavy machinery or driving, but certainly a period of at least several hours. Definitions of impairment while driving vary from state to state and, therefore, specific recommendations about what might legally constitute “impairment” cannot be made in

this study; however, many states declare that the presence of either THC or a metabolite defines a driver as impaired, which will influence the recommendations clinicians make regarding the medical use of THC-containing products.⁵⁸

Conclusion

In a policy regarding medical cannabis, the American Medical Association stated that further trials are necessary to assess the safety and efficacy of medical cannabis, that it not only opposes the legalization of medical cannabis but also supports legislation that provides immunity to physicians who certify that a patient has an approved medical condition or recommend medical cannabis in accordance with their state's laws.⁵⁹ Such policies provide neither guidance regarding the application of current evidence around medical cannabis to clinical practice in states where it is legal nor is there advice for those clinicians who are practicing in environments in which patients will take the substance illicitly, regardless of clinician recommendation. Other professional organizations such as National Hospice and Palliative Care Organization and the American Academy of Hospice and Palliative Care provide educational opportunities regarding medical cannabis but take no official position on its legalization or use. Because the legalization, promotion, and use of medical cannabis is far outpacing research, even those clinicians who do not recommend medical cannabis must still remain informed regarding its purported and substantiated indications and its adverse effects. Even in areas where the evidence for medical cannabis is stronger, several barriers limit its use, including lack of insurance coverage and federal scheduling. Patients who want medical cannabis must pay for it out of pocket, and these costs vary from state to state.⁶⁰

Future studies aim to investigate the role and efficacy of medical cannabis in PC and hospice patients, as well as the general epidemiology of use of medical cannabis in different conditions.^{61,62} This is particularly important as little is known about cannabis use in hospice populations at least in part because many hospices do not inquire about substance use, even if patients are using cannabis therapeutically and not recreationally.⁶³ Federal scheduling and stigmatization of cannabis continues to present a challenge to research, however. Much is known regarding the use of medical cannabis, but there remains much to be discovered.

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